In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

No. 17-642V

Filed: March 15, 2023

ELIZABETH DOLES, Petitioner, v. SECRETARY OF HEALTH AND HUMAN SERVICES, Respondent.	TO BE PUBLISHED Remand; Multiple Sclerosis; Significant Aggravation

Joseph Vuckovich, Maglio Christopher & Toale, P.A., Washington, DC, for Petitioner
Catherine Stolar, U.S. Department of Justice, Washington, DC, for Respondent

DECISION ON REMAND[1]

Oler, Special Master:

On May 16, 2017, Elizabeth Doles ("Petitioner") filed a petition for compensation under the National Vaccine Injury Compensation Program, 42 U.S.C. § 300aa-10, *et seq*.[2] (the "Vaccine Act" or "Program") alleging that the polio and Tdap vaccines she received on April 4, 2016 and April 22, 2016 respectively, caused her to develop acute disseminated encephalomyelitis. Pet. at 1. Petitioner then amended her petition, alleging that her injuries were "best characterized as

[1] This Decision will be posted on the United States Court of Federal Claims' website, in accordance with the E-Government Act of 2002, 44 U.S.C. § 3501 (2012). **This means the Decision will be available to anyone with access to the internet**. As provided in 42 U.S.C. § 300aa-12(d)(4)(B), however, the parties may object to the Decision's inclusion of certain kinds of confidential information. To do so, each party may, within 14 days, request redaction "of any information furnished by that party: (1) that is a trade secret or commercial or financial in substance and is privileged or confidential; or (2) that includes medical files or similar files, the disclosure of which would constitute a clearly unwarranted invasion of privacy." Vaccine Rule 18(b). Otherwise, this Decision will be available to the public in its present form. *Id.*

[2] National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, 100 Stat. 3755. Hereinafter, for ease of citation, all "§" references to the Vaccine Act will be to the pertinent subparagraph of 42 U.S.C. § 300aa (2012).

multiple sclerosis (MS)" and that the vaccines she received either caused or significantly aggravated her condition. Am. Pet. at 2.

After a complete review of the record and for the reasons discussed in this decision, I find that Petitioner has not presented preponderant evidence that the Tdap and/or polio vaccines can cause the significant aggravation of multiple sclerosis. Accordingly, her petition is dismissed.

I. Relevant Medical History

Petitioner was 67 years old and in relatively good health prior to receiving her allegedly causal polio vaccine on April 4, 2016 and Tdap vaccine on April 22, 2016. Petitioner had a past medical history of Graves' disease resulting in hypothyroidism, a hysterectomy, dyslipidemia, a thyroidectomy, and eye surgeries for proptosis and ptosis. Ex. 10 at 36.

In preparation for traveling with the Peace Corps, Petitioner received her polio vaccine on April 4, 2016 from her primary care physician ("PCP") Dr. Arkadiy Shraytman. Ex. 1 at 1; Ex. 14 at 52. Petitioner received a Tdap vaccine on April 22, 2016. Ex. 1 at 2; Ex. 14 at 50.

On June 5, 2016, Petitioner went to the Capital Health Regional Medical Center for what was described as "TIA" (transient ischemic attack). Ex. 8 at 2. Petitioner reported a two-day history of pain in her right upper extremity which she described as achy, as well as shoulder pain, neck stiffness, and weakness in her right grip. *Id.* Petitioner underwent a head CT which did not show any acute changes but did reveal chronic lacunar infarctions.[3] *Id.*

On the same day, Petitioner visited Dr. Kristen Carr, who noted Petitioner reported onset of right arm weakness about 24 hours ago and came in because her arm felt funny, heavy and weak. Ex. 8 at 39. Petitioner also recalled that her handwriting had been different since onset and her arm felt itchy two hours ago with observed redness on the right shoulder. *Id.* Petitioner was discharged on the same day.

On June 6, 2016, Petitioner returned to the Capital Health Regional Medical Center emergency department for "right upper and lower extremity weakness" and was admitted. Ex. 8 at 63, 70-71. Petitioner reported that she returned for right lower extremity weakness that she discovered because she was having difficulty walking. *Id.* at 160. Petitioner's symptoms were discussed with neurologist Dr. Kumar who suspected MS and recommended MRIs. *Id.* at 161.

Petitioner underwent a number of imaging procedures. A cervical spine MRI revealed the following:

[3] Lacunar infarction: a small (less than 1.5 cm) infarct in the brain, found most often in the basal ganglia, internal capsule, pons, or white matter and usually in older hypertensive patients or diabetics. Depending on their location, these may be asymptomatic or may cause significant impairment; those with symptoms are called *lacunar strokes.* When multiple infarcts are present, the condition is called *status lacunaris.* Called also *lacune.* https://www.dorlandsonline.com/dorland/definition?id=82499 (last accessed March 8, 2023).

> Enhancing lesion in the right lateral column at C3-C4 is compatible with active demyelinating disease. Multilevel degenerative change in the cervical spine, most marked at C5-C6 where there is moderate spinal canal stenosis. Foraminal stenosis is the most marked on the left at C4-C5 and on the right at C5-C6. Enhancing lesions in the C3 vertebral body and left articular pillar are indeterminate. A lesion at T2 is also indeterminate but may represent an atypical hemangioma.[4]

Ex. 8 at 112. A thoracic spine MRI revealed "mild degenerative changes in the thoracic spine" but "no abnormal signal or enhancement." *Id.* at 113. The MRI further revealed that "lesions within the T2 and T6 vertebral bodies are indeterminate." *Id.* at 114. Finally, a lumbar spine MRI revealed degenerative changes and noted that "[t]here may be impingement upon transiting right L4 nerve root and bother L5 nerve roots. Clinical correlation is suggested. Lesions with the L1 vertebral body does not completely suppress on STIR and demonstrates mild peripheral enhancement. This may represent an atypical hemangioma." *Id.* at 118.

A brain MRI revealed "[m]ultiple regions of white matter T2/FLAIR hyperintensity… mostly in the periventricular regions as well as subcortically, and many oriented perpendicular to the ependymal[5] surface. None of these lesions demonstrates enhancement." Ex. 8 at 119.

Petitioner's head CT found "no acute intracranial findings" but "there is a chronic-appearing defect in the right greater than left lamina papyracea.[6] The right maxillary sinus is completely opacified with hyperattenuating material, compatible with inspissated mucous." Ex. 8 at 122.

Petitioner's medical records during her stay indicated her doctors believed that she was experiencing an acute multifocal demyelinating or MS disease. *See* Ex. 8 at 76. Alternative diagnoses include Lyme disease or CNS vasculitis. *See id.* Petitioner had not experienced a TIA or stroke. *Id.*

On June 11, 2016, Petitioner visited Dr. Michael Beede for a rheumatology consultation. Ex. 8 at 64-66. Dr. Beede was consulted due to Petitioner's positive ANA, her history of Graves' disease and "new multiple sclerosis." *Id.* at 64. Petitioner had been treated with IV "pulse steroids" for five days and had moderately improved. *Id.* Dr. Beede believed Petitioner needed to undergo

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[4] Hemangioma: 1. a common type of vascular malformation, usually seen in infancy and childhood, consisting of newly formed blood vessels that result from malformation of angioblastic tissue of fetal life. There are two main types: capillary hemangiomas and cavernous hemangiomas. 2. a general term denoting a benign or malignant vascular malformation that resembles the classic type of hemangioma but occurs at any age. https://www.dorlandsonline.com/dorland/definition?id=21700&searchterm=hemangioma (last accessed March 13, 2023).

[5] Ependyma: the lining membrane of the ventricles of the brain and of the central canal of the spinal cord. https://www.dorlandsonline.com/dorland/definition?id=16737 (last accessed March 8, 2023).

[6] Lamina papyracea, also known as the orbital lamina is the orbital plate of ethmoid bone: a thin plate of bone laterally bounding the ethmoid labyrinth on either side and forming part of the medial wall of the orbit. https://www.dorlandsonline.com/dorland/definition?id=84310 (last accessed March 8, 2023).

additional bloodwork to rule out Lupus and Hashimoto's disease but believed she otherwise did not need a rheumatology follow up.

Petitioner was discharged from Capital Health Regional Medical Center and transferred to the St. Lawrence Rehabilitation Center on June 14, 2016. Ex. 4 at 11. Her physical examination revealed she had decreased right upper extremity strength and grip strength graded at 3+/5, decreased fine motor control, and right lower extremity was 4/5 compared to left; Petitioner was able to walk with assistance and had decreased balance. *Id.* Petitioner was discharged from the rehabilitation center on June 24, 2016.

On June 23, 2016, Petitioner was seen by neurologist Dr. Chirag Shukla "for right-sided weakness." Ex. 2 at 3-4. Dr. Shukla observed mild limping in the right leg and recommended a complete work up for a diagnosis. *Id.* at 3.

On July 6, 2016, Petitioner presented to neurologist Dr. Chitharanjan Rao. Ex. 4 at 8-9. Dr. Rao noted that Petitioner had a nearly normal gait but was still experiencing right upper extremity weakness that presented when Petitioner was writing. *Id.* at 8. Petitioner also reported paresthesias in the left upper extremity, numbness in her left hand, and hyperpathia.[7] *Id.* Dr. Rao's assessment was "Likely ADEM, probably related vaccination. So far a monophasic event. A possibility of multiple sclerosis to be considered, although so far she does not appear to fulfill clinical or diagnostic criteria for the same." *Id.* at 9. Petitioner had a normal neurological exam, other than mild sensory loss in the left hand and diffuse hyperreflexia.[8] Ex. 14 at 21.

On July 14, 2016, Petitioner followed up with Dr. Shukla. Ex. 2 at 2. Her work up returned with positive oligoclonal bands, but other results were either negative or normal. *Id.* It was Dr. Shukla's impression that Petitioner had MS. *Id.*

On July 19, 2016, Petitioner underwent a visual evoked exam which revealed a latency on Petitioner's right side, which was "indicative of a conduction delay in the visual pathways on the right, anterior to the optic chasm." Ex. 4 at 52. Petitioner also underwent a battery of nerve tests, all of which were non-diagnostic. Ex. 14 at 11-16.

On July 25, 2016, Petitioner returned to St. Lawrence Rehabilitation Center for "OP OT s/p MS exacerbation." Ex. 4 at 43-47. The assessment noted that Petitioner had "made progress this month by improving [upper extremity] strength" but still has "mild deficits in [right] dominant shoulder strength and fine/gross motor coordination which limit full independence." *Id.* at 46.

Petitioner returned to Dr. Rao on July 28, 2016 for a follow-up. Ex. 3 at 6-8. Dr. Rao maintained that Petitioner's diagnosis was like ADEM but MS was a possibility. *Id.* at 7. Dr. Rao

[7] Hyperpathia: abnormally exaggerated subjective response to painful stimuli. https://www.dorlandsonline.com/dorland/definition?id=23940 (last accessed March 8, 2023).

[8] Hyperreflexia: disordered response to stimuli characterized by an exaggeration of reflexes. https://www.dorlandsonline.com/dorland/definition?id=23992&searchterm=hyperreflexia (last accessed March 13, 2023).

recommended additional MRIs in September and recommended that Petitioner "avoid vaccinations this season." *Id.*

On August 10, 2016, Petitioner was discharged from physical therapy at the St. Lawrence Rehabilitation Center. Ex. 6 at 5-6. Petitioner met her PT goals and was given a home exercise program ("HEP"). *Id.* at 5, 6. Petitioner had 13 physical therapy sessions in total. *Id.* at 7.

On August 19, 2016, Petitioner visited Dr. Rao with updated MRIs performed on August 17, 2016. Ex. 4 at 1-2. Dr. Rao noted that the cervical spine MRI revealed

> ovoid area of abnormal signal, with associated enhancement and expansion on the right side of the spinal cord at C3-4 level has enlarged in size. This is compatible with a demyelinating process related to patient's history of multiple sclerosis…. Spondylotic changes of the cervical spine are re-demonstrated as well as cervical spine lesions, unchanged since the prior study.

Id. at 2. The brain MRI revealed "Stable FLAIR hyperintense lesions in the supratentorial white matter without associated mass effected or abnormal enhancement, compatible [with] patient's history [of] multiple sclerosis." *Id.* Dr. Rao noted that "CSF exam showed no oligoclonal bands; rest of the studies were somewhat unreliable as lumbar puncture was traumatic." *Id.*

Dr. Shraytman filed a VAERS report on August 22, 2016. *See* Ex. 14 at 35-36 (Dr. Shraytman's 8/23/2017 letter from the Department of Health & Human Services regarding his VAERS report filed a year ago for Petitioner's Tdap vaccine; the original VAERS report is not included in the record). Dr. Shraytman's VAERS report recounted that Petitioner developed an "acute demyelinating episode" after Tdap vaccine. *Id.* at 35.

On September 7, 2016, Petitioner visited the Capital Health Regional Medical Center emergency department for "transient right hemiparalysis." Ex. 8 at 362-67. The history of present illness details that Petitioner had a history significant for "acute demyelinating disorder secondary to Tdap or Polio vaccine give in April." *Id.* at 362. Petitioner's symptoms started one hour prior to arriving at the emergency department and were described to be moderate-severe, with some minimal paresthesias in the right upper extremity and were similar to her symptoms in June. *Id.* Petitioner's symptoms resolved and she was discharged. *Id.* at 362-63.

Between September 7 and 20, 2016, Petitioner moved from her residence in New Jersey to Massachusetts and established new care with different physicians.

On September 20, 2016, Petitioner visited the Beth Israel Deaconess Medical Center emergency department. Ex. 10 at 14-15. Petitioner's HPI noted that she experienced right hand, arm, and leg shaking episode that lasted less than one minute, but she had been experiencing these episodes for the past three months. *Id.* at 14. Petitioner also reported that her MRI showed a demyelinating lesion, but an EEG had not been performed, and had been told she either had MS or ADEM. *Id.* Petitioner did not have any abnormalities on examination and was discharged the same day. *Id.* at 16. Petitioner was recommended to follow up with a neurology consultation. *Id.* at 20.

On September 27, 2016, Petitioner visited neurologist Dr. Slavenka Kam-Hansen at the Beth Israel Deaconess Medical Center. Ex. 10 at 33-35. Petitioner informed Dr. Kam-Hansen that she first experienced a left lower leg burning sensation after her Tdap and polio vaccines in April. *Id.* at 33. Her physical and neurological exams were normal. *Id.* at 33-34.

On September 29, 2016, Petitioner began seeing Dr. Harvey Bidwell as her new PCP in Massachusetts. Ex. 10 at 36-40. Petitioner gave Dr. Bidwell a detailed medical history, which included:

> About June 5th after having some right shoulder stiffness she developed severe spasticity /? Weakness right upper extremity and then right leg along with ferocious itching. Prior to June 5 she had some hot spots on legs include left leg of numbness.
>
> She was initially diagnosed as having MS by three neurologists and then saw a neurologist in whom she now has a lot of confidence who diagnosed her as having [ADEM].
>
> Symptoms now much less. Still has some weakness [right upper extremity]. Not much weakness right leg now. She does get some dysesthesias and periodically right upper extremity goes into acute cramp.
>
> She was recently evaluated in ED for what there was felt by neurologist to be a focal seizure. She has been started on gabapentin and is now taking 300mg tid.[9]

Id. at 36-39.

On November 16, 2016, Petitioner followed up with Dr. Kam-Hansen. Ex. 15 at 15-17. Petitioner's symptoms during this visit included a burning sensation in her left shin and the arch of her foot, as well as a painful sensation on her left hip when touched. *Id.* at 15. Petitioner also had sensitivity to coldness, which she perceived as a burning sensation. *Id.* On Petitioner's right side, she stated she was experiencing a "throbbing, achy and pins and needles sensation" from her shoulder to fingertips and that she was also experiencing fatigue despite getting eight hours of sleep. *Id.* Petitioner also informed Dr. Kam-Hanson of a pending lawsuit "apparently for all individual who are [symptomatic] six months after their vaccination." *Id.* It was Dr. Kam-Hansen's assessment that Petitioner "has ADEM rather than MS. However only with time this will become a clearer diagnosis." *Id*. at 16. Dr. Kam-Hansen recommended that Petitioner have additional MRIs and follow up again in four months. *Id.* at 17.

Petitioner returned to Dr. Kam-Hansen on December 1, 2016 to review her brain and cervical spine MRIs. Ex. 15 at 18-20. Petitioner's MRIs showed "unchanged brain lesions and diminished cervical cord lesion of the right aspect of the C3 and C4 cord without evidence of abnormal enhancement. No new lesions are noted in the cervical and thoracic spine. Multilevel

[9] T.I.D.: ter in di´e (three times a day). https://www.dorlandsonline.com/dorland/definition?id=50067 (last accessed March 8, 2023).

cervical spondylosis[10] was found." *Id.* at 18. Dr. Kam-Hansen cautioned Petitioner against traveling abroad, especially to tropical climates, as there were risks of worsening her condition. *Id.* at 20. She recommended that Petitioner follow up in a few months. *Id.*

On March 30, 2017, Petitioner visited Dr. Kam-Hansen for a follow-up. Ex. 15 at 30-32. Petitioner reported that she had returned from Indonesia and had not experienced any new issues with her condition during her travel. *Id.* at 30. Petitioner's gabapentin medication dosage was lowered. *Id.* at 32.

On March 12, 2019, Petitioner visited Dr. Kam-Hansen. Ex. 50 at 30-32. Petitioner requested a referral for physical therapy to improve leg strength and balance, and a note to be excluded from receiving any vaccines mandated by her part time job. *Id.* at 30. Petitioner informed Dr. Kam-Hansen that "Compensation for vaccine complications has not yet been settled." *Id.*

Petitioner was seen on March 27, 2019 complaining of right arm paresthesias she had been experiencing the past few days and some right shoulder pain. Ex. 51 at 2-3, 66-68. Petitioner also reported she was stressed "because of some lawsuit issues involving her suit against the federal government." *Id.* at 3. Petitioner's neurological exam was normal. *Id.* at 67.

Other medical records were filed but are not relevant to the injury alleged in this case.

II. Expert Opinions and Qualifications

A. Petitioner's Expert – Slavenka Kam-Hansen, MD, PhD

1. Qualifications

Dr. Kam-Hansen completed her medical degree at the University of Belgrade in the former Yugoslavia in 1972. Ex. 18 at 2. She earned her PhD in neurology at the University of Linkoping in Sweden in 1980. *Id.* She is an attending neurologist at Beth Israel Deaconess Medical Center in Boston and an instructor in the Department of Neurology at Harvard Medical School. *Id.* at 2-3. Dr. Kam-Hansen is board certified in neurology. *Id.* at 6. She is the author of 34 peer-reviewed journal articles and 16 book chapters in neurology. *Id.* at 9-13.

2. Treating Physician Letter

Dr. Kam-Hansen submitted a two-page letter describing her evaluation of Petitioner's condition ("Kam-Hansen Letter"). She stated that, on examination, she found Petitioner to be experiencing "pain, sensory changes, and fatigue," as well as "sensory changes in her left leg." Kam-Hansen Letter at 1. Dr. Kam-Hanson opined that, based on the temporal relationship between vaccination and symptom onset and the lack of any neurological symptoms prior to vaccination, ADEM was the most likely diagnosis. *Id.* Dr. Kam-Hansen felt that it was unlikely that Petitioner had MS because patients with MS normally begin to experience symptoms in their 30s or 40s. *Id.*

[10] Spondylosis: degenerative spinal changes due to osteoarthritis. https://www.dorlandsonline.com/dorland/definition?id=46749&searchterm=spondylosis (last accessed March 13, 2023).

Dr. Kam-Hansen opined that "it is highly likely that two vaccinations [Petitioner] received in April of 2016…caused her to develop ADEM and the sequelae from which she continues to suffer." Kam-Hansen Letter at 2. She went on to opine that Petitioner's history of Graves' disease made her more susceptible to developing other autoimmune conditions such as ADEM. *Id.* She recommended that Petitioner receive no further vaccinations. *Id.*

B. Petitioner's Expert – John Steel, MD

1. Qualifications

Dr. Steel received his medical degree from the University of North Carolina in 1977. Ex. 21 at 1. He is board certified in neurology. *Id.* Prior to his retirement in 2017, he was the neurology section chief at Coastal Carolina Health Care. *Id.* at 2. He was a practicing neurologist for nearly 40 years. *Id.* Dr. Steel was involved in 14 different pharmaceutical trials between 1997 and 2010. *Id.* at 3-4. He has also provided expert opinion or testimony in 34 civil cases since 2013. *Id.* at 4-7.

2. First Expert Report

In his first expert report, Dr. Steel opined that Petitioner "experienced an attack of focal myelitis (inflammation of the spinal cord), caused by neuroimmune activation from receiving two vaccinations in close proximity." Ex. 20 (hereinafter "First Steel Rep.") at 3. He further opined that Petitioner meets the current diagnostic criteria for MS and that her MS was clinically silent (otherwise known as radiographically isolated syndrome or "RIS") until the vaccines "unmasked" it. *Id.*

Dr. Steel opined that the onset of Petitioner's symptoms in June 2016 was a clinically isolated event, or "the first episode of neurological symptoms typical of an MS relapse in a person not known to have MS." First Steel Rep. at 3. He opined that the lesion on Petitioner's spinal cord is typical of those found in cases of focal spinal myelitis and is "radiographically typical for an MS plaque in the spinal cord." *Id.*

Dr. Steel acknowledged that vaccines rarely cause or exacerbate MS. First Steel Rep. at 4. However, he explained that there is evidence that vaccines can trigger autoimmune demyelination in people who are genetically or otherwise susceptible. *Id.* He cited a paper in which 71 cases of post-vaccination inflammatory demyelinating syndromes were reported between 1979 and 2013. *Id.* (citing Karussis & Petrou, *The spectrum of post-vaccination inflammatory CNS demyelinating syndromes*, 13 AUTOIMMUNITY REVS. 215-24 (2014) (filed as Ex. 36) (hereinafter "Karussis & Petrou")). Roughly one third of these cases reported symptom onset more than three weeks after vaccination. *Id.* Because MS was not among the syndromes reported in this study, Dr. Steel asserted that "MS, a chronic, recurrent, and progressive disorder, is not likely caused by any single immune insult event," and furthermore that "it is likely that triggering of clinically significant MS by vaccines is underreported for this reason." *Id.*

Dr. Steel reiterated his opinion that Petitioner suffered an attack of focal spinal myelitis due to the vaccines because of an underlying susceptibility, clinically silent MS. First Steel Rep. at 5. Dr. Steel suggested that the mechanism at work in Petitioner's case may have been "molecular mimicry, epitope spreading, bystander activation, T-helper cell activation, [or] cytokine induction." *Id.* He opined that, while there is little evidence supporting the idea that vaccines cause MS, there is evidence to suggest that vaccines can trigger single attacks of demyelination, and "there is good reason to think that such an event is more likely in patients with subclinical MS." *Id.*

3. Second Expert Report

Dr. Steel began his second expert report by clarifying that he and Dr. Sriram are in agreement on three points: 1) that Petitioner does not meet the diagnostic criteria for ADEM; 2) that Petitioner has MS; and 3) that the vaccines Petitioner received did not cause her MS. Ex. 54 (hereinafter "Second Steel Rep.") at 1.

Dr. Steel opined that Petitioner suffered an attack of transverse myelitis ("TM") that caused her previously clinically silent MS to become symptomatic, but added that "[Petitioner's] MS is a red herring and has served to confuse the issue." Second Steel Rep. at 1.

Dr. Steel explained that immune mediated demyelinating disorders exist on a spectrum, and that all of them involve activation of the immune system causing attacks on one or more components of myelin. Second Steel Rep. at 2. He explained that causation is likely multifactorial, and that some contributing factors may include "genetic predisposition, environment, nutritional status, comorbidities, and exposure to various triggers." *Id.*

Dr. Steel next explained the characteristics of TM and opined that Petitioner meets all of the inclusion and exclusion criteria "except that her symptoms and signs were unilateral." Second Steel Rep. at 3. He also cited medical literature which suggests that, while TM is typically bilateral, unilateral and asymmetrical presentations occur. *Id.* (citing Frohman & Wingerchuk, *Transverse Myelitis*, 363 N. ENGL. J. MED. 564 (2010) (filed as Ex. 39) (hereinafter "Frohman & Wingerchuk")). Dr. Steel also explained that cases of TM fall into two categories, acute complete transverse myelitis ("ACTM") and acute partial transverse myelitis ("APTM"), where complete and partial refer to the degree of damage to the spinal cord (i.e., encompassing the full transverse anatomy of the spinal cord and less than the full transverse anatomy of the spinal cord, respectively). *Id.* Dr. Steel noted that APTM is strongly correlated with MS, "either as an initial presenting disease or as part of the ongoing relapsing-remitting course of MS." Dr. Steel opined that Petitioner had an attack of APTM. *Id.*

Dr. Steel explained that the most common cause of TM is viral infection. Second Steel Rep. at 3. He acknowledged that epidemiologic studies have not found convincing evidence that vaccines cause TM but pointed out that short series and case reports do provide some evidence of causation. *Id.* at 4. Dr. Steel also noted that the 2014 edition of the International Classification of Diseases, or ICD-10, includes a diagnostic code for post-immunization/post-vaccinal myelitis. *Id.* at 5.

Dr. Steel cited medical literature arguing that "'immunization may also trigger attacks of myelitis in the context of an underlying disease (especially multiple sclerosis or neuromyelitis optica).'" Second Steel Rep. at 5 (quoting Frohman & Wingerchuk). He also discussed medical literature that examined 780 cases of CNS acute demyelinating syndromes following vaccination. *Id.* (citing Langer-Gould et al., *Vaccines and the Risk of Multiple Sclerosis and Other Central Nervous System Demyelinating Diseases*, 71 JAMA NEUROL 12, 1506-13 (2014) (filed as Ex. 62) (hereinafter "Langer-Gould")). This study did not find that vaccines had any long-term effect on demyelinating disease but did find a strong short-term effect on subjects younger than 50 years of age. *Id.* (citing Langer-Gould). The authors found that 24 of the 780 subjects experienced their first attack of acute demyelinating disease within 30 days of vaccination, concluding that "'at most, vaccines are enhancers of preexisting autoimmunity.'" *Id.* (quoting Langer-Gould). Based on this evidence, Dr. Steel opined that "it is reasonable to consider that at-risk individuals, such as [Petitioner], are more likely to develop complications following vaccination." *Id.* at 6.

Dr. Steel next pointed out that the package insert for the Tdap vaccine Petitioner received advises that "'progressive or unstable neurological conditions… are reasons to defer vaccination with a pertussis-containing vaccine'" and that it is unknown whether vaccination "'might hasten manifestations of the disorder or affect the prognosis.'" Second Steel Rep. at 6 (quoting Ex. 59, Tdap package insert).

Dr. Steel summarized the onset of Petitioner's condition as the development of an acute inflammatory demyelinating event approximately five weeks post-vaccination. Second Steel Rep. at 6. He noted that subsequent testing revealed that Petitioner's brain contained lesions, "likely old, and clinically silent." *Id.* Dr. Steel opined that Petitioner "had several risk factors for developing an inflammatory demyelinating disorder: female sex, Caucasian race, and concomitant autoimmune disorders (Graves' disease and silent MS)." *Id.* He opined that it is very likely that the vaccinations she received "altered her biological equilibrium," causing her clinically silent MS to become overt. *Id.* He noted that epidemiological studies tend to focus on one vaccine or one brand of product, and that there is no data on how receipt of multiple vaccines in a short period, as in Petitioner's case, might impact underlying MS. *Id.* at 6-7.

Dr. Steel concluded by opining that Dr. Sriram's expert report had failed to address Dr. Steel's theory that the vaccines "triggered an episode of spinal myelitis in the context of [Petitioner's] pre-existing clinically silent MS." Second Steel Rep. at 7. He also cautioned that epidemiological studies may fail to capture rare adverse events. *Id.*

C. Respondent's Expert – Subramaniam Sriram, MD

1. Qualifications

Dr. Sriram received his medical degree from the University of Madras in India in 1973. Ex. B at 1. Since 1993, he has held dual appointments at Vanderbilt University Medical Center as professor of experimental neurology and professor of pathology, microbiology, and immunology. *Id.* He is the author of 139 peer-reviewed journal articles and 11 book chapters in the field of neuroimmunology with a particular focus on MS. *Id.* at 9-20. Dr. Sriram is board certified in internal medicine and neurology. *Id.* at 1.

2. First Expert Report

In his first expert report, Dr. Sriram began his analysis by explaining the McDonald diagnostic criteria for MS, which require evidence of CNS lesions that are disseminated in both space and time. Ex. A (hereinafter "First Sriram Rep.") at 7. He noted that "[t]he first neurological event (absence of dissemination in time) is referred to as clinically isolated syndrome In a patient later diagnosed with MS, the clinically isolated syndrome constitutes the first attack of the disease." *Id.* Dr. Sriram went on to opine that Petitioner has MS because she meets the diagnostic criteria for both dissemination in time and dissemination in space. *Id.* at 7-8.

Dr. Sriram explained that MS is thought to be caused by an autoimmune process, but the specific auto-antigen is still unknown. First Sriram Rep. at 8. The predominant theory is that MS is mediated by T lymphocytes that target the white matter of the CNS, causing the damage to myelin that leads to impaired nerve conduction and clinical disability. *Id.*

Dr. Sriram stated that the "prevailing opinion among scientists and the medical community is that there is no causal connection between vaccines and the development of acute clinical worsening [of MS], often referred to as relapses." First Sriram Rep. at 9. He cited a literature review that analyzed research on this topic, which found no evidence that vaccines exacerbate MS, and even found some evidence for a decreased risk of MS upon receipt of certain vaccinations, including BCG for tuberculosis. *Id.* (citing Mailand & Frederiksen, *Vaccines and multiple sclerosis: A systematic review,* 264 J. OF NEUROLOGY 1035-50 (2017) (filed as Ex. E) (hereinafter "Mailand & Frederiksen")). Other studies have found evidence of a decreased risk of developing MS after vaccination for diphtheria and tetanus. *Id.* (citing Farez & Correale, *Immunizations and risk of multiple sclerosis: Systematic review and meta-analysis*, 258 J. OF NEUROLOGY 1197-1206 (2011) (filed as Ex. I)). Dr. Sriram noted that "MS patients are a highly studied population" and that no evidence of a vaccine-induced increase in MS exacerbations has been found. *Id.* at 10.

Dr. Sriram next addressed Dr. Kam-Hansen's opinion that Petitioner has ADEM rather than MS. First Sriram Rep. at 10. He disagreed with the diagnosis of ADEM because, in his opinion, Petitioner did not meet the diagnostic criteria in several respects. *Id.* at 11. Specifically, 1) he noted that Petitioner was an older adult rather than a child; 2) that Petitioner had no encephalopathy with her first clinical event; 3) that Petitioner exhibited no behavioral change; 4) that Petitioner's condition improved with steroid therapy; 5) that Petitioner had had no clinical relapses outside of her initial symptoms; 6) that her CNS legions were characteristic of MS rather than ADEM; and 7) that Petitioner's CSF contained oligoclonal bands. *Id.* at 11-13. All of these findings, Dr. Sriram argued, are inconsistent with the diagnostic criteria for ADEM. *Id.* at 11. Dr. Sriram also took issue with Dr. Kam-Hansen's reference to Petitioner's age as making ADEM the more likely diagnosis. *Id.* at 13. He pointed out that some studies have found an increase in MS cases among women over the age of 50, and that ADEM is most common in children under the age of 10. *Id.* He argued that these two points weigh in favor of a diagnosis of MS rather than ADEM. *Id.*

Dr. Sriram next responded to Dr. Steel's first expert report. First Sriram Rep. at 13-14. Dr. Sriram disagreed with Dr. Steel's position that vaccines can trigger autoimmune demyelination in

people who are already susceptible. *Id.* at 13-14. He criticized Dr. Steel's evidence, pointing out that the medical literature Dr. Steel cited on this point does not pertain to MS. *Id.* at 14. Dr. Sriram also took issue with Dr. Steel's statement that vaccines can trigger an immune response in the CNS, particularly in individuals with an ongoing autoimmune process. *Id.* Dr. Sriram argued that "it does not follow that any vaccine is capable of inducing any inflammatory demyelinating disease" and criticized the medical literature Dr. Steel cited because it pertained to vaccines other than those that Petitioner received. *Id.*

Dr. Sriram concluded by opining that "[o]ther than offering a temporal relationship between [Petitioner's] receipt of the Tdap and polio vaccines and the development of clinical and new MRI lesions, Dr. Steel does not provide a biological basis on which vaccines can cause a worsening of MS." First Sriram Rep. at 16. He opined that the vaccines Petitioner received "played no role in the development of a clinical relapse of MS." *Id.*

3. Second Expert Report

In his second expert report, Dr. Sriram criticized Dr. Steel's second expert report, saying that "Dr. Steel is now attempting to re-define the myelitic syndrome that is a characteristic feature of MS as a separate disease entity with a different etiology." Ex. O (hereinafter "Second Sriram Rep.") at 1. He argued that, according to the principle of clinical parsimony (also known as "Occam's Razor"), it is prudent to interpret the onset of Petitioner's symptoms as part of the underlying MS disease process rather than a separate process. *Id.* He argued that Dr. Steel was confusing the issue by "trying to invoke an alternative etiology for transverse myelitis, when none is evident." *Id.*

Dr. Sriram observed that Dr. Steel seems to argue Petitioner's myelitis was not due to her underlying MS, even though myelitis is part of the MS syndrome. Second Sriram Rep. at 2. He added that Dr. Steel's opinion seems to be that "absent her myelitis, [Petitioner's] clinically silent MS would never have become 'unmasked.'" *Id.*

Dr. Sriram opined that, according to the diagnostic criteria proposed by the Transverse Myelitis Working Group in 2002, Petitioner is excluded from a diagnosis of idiopathic TM. Second Sriram Rep. at 2. The reason for this, he argued, is that the Working Group identified brain MRI abnormalities suggestive of MS, which Petitioner exhibited, as one of the exclusionary criteria for idiopathic TM because it fits better with a diagnosis of disease-based TM (i.e., TM is part of the underlying MS disease process rather than a separate disease process). *Id.* at 2-3. Dr. Sriram pointed out that these exclusionary criteria were developed in recognition of the differences in treatment protocols for patients with idiopathic TM and those, like Petitioner, who experienced an attack of acute TM and were later diagnosed with MS. *Id.* at 2.

Dr. Sriram opined that Dr. Steel's observation that MS and TM are strongly associated actually supports Dr. Sriram's opinion that Petitioner's TM was a part of her underlying MS disease process. Second Sriram Rep. at 3. He cited medical literature which concluded that, in patients who are later diagnosed with MS, an attack of TM can constitute the clinically isolated syndrome that makes clinically silent MS become symptomatic. *Id.* (citing Krupp et al., *Consensus definitions proposed for pediatric multiple sclerosis and related disorders*, 68 NEUROLOGY Suppl 2, 1-6 (2007) (filed as Ex. L)).

Dr. Sriram next opined that Dr. Steel's expert reports conflate myelitic syndrome in MS patients with idiopathic TM. Second Sriram Rep. at 3. He argued that the medical literature does not contain compelling evidence of vaccines causing TM, and that the evidence Dr. Steel cited was anecdotal and did not relate to TM in patients with MS. *Id.* at 4. Dr. Sriram pointed out that one of the papers Dr. Steel cited makes the distinction between disease-associated TM and postvaccination TM and counsels against overreliance on case reports. *Id.*

Dr. Sriram also criticized Dr. Steel's reliance on Frohman & Wingerchuk, opining that the authors do not provide support for their claim that vaccination can cause TM in a patient with underlying MS. Second Sriram Rep. at 4; Frohman & Wingerchuk. He argued that no new evidence showing that vaccines can aggravate TM or any other acute demyelinating syndrome has come to light in the years since the paper was published. *Id.* He further argues that the authors of this study contradict themselves by differentiating between postvaccination TM and TM in patients with MS and also claiming that vaccines can trigger TM in patients with MS. *Id.* at 5.

Dr. Sriram criticized Dr. Steel's reliance on Langer-Gould. Second Sriram Rep. at 5; Langer-Gould. He argues that the evidence of an association between vaccines and acute demyelinating syndromes in younger patients within 30 days of vaccination does not support Petitioner's claim because petitioner is 67 years old and her onset was roughly 45 days after she received the second vaccine. *Id.*

Dr. Sriram also disagreed with Dr. Steel's opinion that the vaccine package insert is relevant in this case. Second Sriram Rep. at 6. He noted the manufacturer's statement in the insert that "'[b]ecause these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a relationship to the vaccine.'" *Id.* (quoting Tdap package insert, Ex. 59). He also opined that the adverse events reported in the package insert are expressed in broad terms such as "nervous system disorders" and "myelitis" and are thus too vague to apply to Petitioner's specific case of TM in the context of MS. *Id.*

Dr. Sriram concluded by opining that Dr. Steel's opinion that the vaccines altered Petitioner's biological equilibrium, resulting in an "unmasking" of her MS, lacks a scientific foundation. Second Sriram Rep. at 6. He argued that Dr. Steel's opinion also collapses the distinction between idiopathic TM and disease-associated TM. *Id.*

III. Procedural History

Petitioner filed her original petition on May 16, 2017. ECF No. 1. She alleged that the polio and Tdap vaccines she received on April 4, 2016 and April 22, 2016 caused her to develop acute disseminated encephalomyelitis ("ADEM"), or in the alternative, that these vaccines significantly aggravated her condition. *Id.* at 1-2. On July 5, 2019, Petitioner filed an amended petition, specifically stating that her injuries "are best characterized as multiple sclerosis (MS)." Am. Pet. at 2. She alleged that the vaccines she received either caused or significantly aggravated her MS. *Id.*

In 2019 and 2020, Petitioner filed two expert reports from Dr. Steel. Exs. 20, 54, while Respondent countered with two reports from his expert, Dr. Sriram. Exs. A, O.

The parties then briefed the case for a ruling on the record. On July 29, 2020, Petitioner filed a Motion for a Findings of Fact and Conclusion of Law and a memorandum in support of her motion. ECF Nos. 67, 68. Respondent file a response to Petitioner's motion on October 27, 2020. ECF No. 70. Petitioner filed a reply on December 4, 2020. ECF No. 72.

On February 1, 2021, the special master previously assigned to this case issued a Ruling on Entitlement; ECF No. 71; *Doles v. Sec'y of Health & Hum. Servs.*, No. 17-642V, 2021 WL 750416 (Fed. Cl. Spec. Mstr. Feb. 1, 2021) (hereinafter "First Entitlement Ruling"). The parties then resolved damages and the special master issued a damages decision. *Doles v. Sec'y of Health & Hum. Servs.*, No. 17-642V, 2021 WL 5055851 (Fed. Cl. Spec. Mstr. Oct. 5, 2021); ECF No. 84.

On November 4, 2021, Respondent filed a Motion for Review of the special master's entitlement ruling. ECF No. 86. Petitioner filed a response on December 6, 2021. ECF No. 89. On February 23, 2022, the Court held oral arguments via Zoom. *See* Minute Entry dated February 23, 2022.

The Court issued an opinion and order vacating the First Entitlement Ruling and remanding the case back to the special master. *Doles v. Sec'y of Health & Hum. Servs.*, 59 Fed. Cl. 241 (2022); ECF No. 90 (hereinafter "*Doles I*"). The Court concluded that the special master's analysis of the case pursuant to a significant aggravation theory was improper in that he "adopted a theory of injury and causation that Petitioner never advanced and that does not appear to have been obvious from the evidence submitted." *Doles I* at 246. The Court also held that "the Special Master's Ruling misinterpreted its primary medical authority, the Langer-Gould study." *Id.* at 247. The Court directed that the special master consider the parties' arguments on significant aggravation of MS and "re-evaluate the medical evidence under the correct legal and scientific standards." *Id.* at 249. The Court also instructed that "[o]n remand, the Special Master should give the parties the opportunity for briefing – and, if appropriate, new written or live evidence – on whether Petitioner's vaccinations aggravated her MS." *Id.*

The originally assigned special master conferred with the parties and directed that they file briefs pursuant to the theory of significant aggravation. ECF Nos. 94, 97-99. The parties agreed to forego the opportunity to file supplemental expert reports. ECF No. 94. The special master then issued a second Ruling on Entitlement; ECF No. 102; *Doles v. Sec'y of Health & Hum. Servs.*, No. 17-642V, 2022 WL 3229286 (Fed. Cl. Spec. Mstr. June 24, 2022) (hereinafter "Second Entitlement Ruling").

Respondent filed another Motion for Review of the special master's Second Entitlement Ruling on July 22, 2022. ECF No. 105. Petitioner filed a response on August 22, 2022. ECF No. 109. The Court held oral argument on October 31, 2022 (*see* Minute Entry dated November 8, 2022) and then issued his second opinion and order vacating the Second Entitlement Ruling and remanding the case back to the Office of Special Masters. The Court found that the special master's interpretation of Dr. Steel's opinion in his Second Entitlement Ruling departed from the interpretation he previously articulated in in his First Entitlement Ruling. *Doles v. Sec'y of Health*

& Hum. Servs., 163 Fed. Cl. 726, 731 (2022) (hereinafter "*Doles II*"); ECF No. 113. The Court found that this change in position was arbitrary and capricious, and directed that the case be assigned to a different special master. *Id.* at 733. In the second Opinion and Order, the Court further directed that the new special master "consider the record anew." *Id.* The Court instructed that "[t]he evidentiary record shall not be supplemented on remand." *Id.*

The Chief Special Master assigned the case to my docket on December 19, 2022. ECF No. 114, 115.

On December 21, 2022, Petitioner filed a Motion for Reconsideration asking the Court to reconsider its direction that the case be assigned to a new special master. ECF No. 116. Respondent filed a response on December 30, 2022. ECF No. 118. Petitioner filed a reply on January 6, 2023. ECF No. 120. The Court issued an order denying Petitioner's motion for reconsideration on January 10, 2023. ECF No. 121.

I conducted an oral argument on February 2, 2023. I asked the parties to discuss two questions: 1) whether I was permitted to consider the Langer-Gould study on remand; and 2) whether Dr. Steel had articulated a theory of significant aggravation in his two expert reports. ECF No. 128. During oral argument, Respondent argued that I was not permitted to consider the Langer-Gould study pursuant to the doctrine of law of the case. ECF No. 128 at 22-27. Petitioner largely agreed with Respondent's position on this matter, except to note that I am permitted to consider portions of the study not discussed by the Court. *Id.* at 7-14. Respondent further maintained that Dr. Steel had not articulated a theory of significant aggravation in either of his expert reports. Petitioner disputed this position. I did not order that the parties complete additional briefing, and the parties did not request the opportunity to file briefs. Accordingly, this case is now ripe for adjudication.

IV. Preliminary Issues

In any remanded case, the special master is bound by the determinations of the Court on matters of law and fact. *Rickett v. Sec'y of Health & Hum. Servs.*, 468 F. App'x 952, 959 (Fed. Cir. 2011) (quoting *Hanlon v. Sec'y of Health & Hum. Servs.*, 40 Fed. Cl. 625, 630 (Fed. Cl. 1998)).

A. The Parties Agree that Petitioner Suffers from MS

Although Petitioner initially contended that her vaccinations either caused her to develop ADEM or significantly aggravated that condition, she filed an amended petition clarifying that her correct diagnosis is MS. Dr. Steel and Dr. Sriram both agree that MS is Petitioner's correct diagnosis. Accordingly, I find that Petitioner's MS diagnosis is supported by preponderant evidence.

Before substantively analyzing the case, I will address two preliminary issues, both of which were discussed during oral argument on February 2, 2023. First, am I permitted to consider the Langer-Gould study in my analysis of this case? Second, has Petitioner presented evidence of significant aggravation through her expert, Dr. Steel? I will address each issue in turn.

B. The Langer-Gould Study

In his First Entitlement Ruling, the previous special master found the Langer-Gould study to be particularly persuasive in enabling Petitioner to establish *Loving* prong four. *See* First Entitlement Ruling at *17 (calling Langer-Gould the one "especially relevant and persuasive study related to significant aggravation of MS."). The Court disagreed, finding that the previous special master improperly relied upon Langer-Gould in finding Petitioner entitled to compensation because the study found no association between vaccines and MS; and further, because the association between vaccination and demyelinating conditions was only observed in patients younger than 50 who developed the condition within 14 days of vaccination. *Doles I* at 247. The Court ultimately concluded that "[a] finding of causation would have to be *despite* the Langer-Gould study, not *because* of it." *Id.* at 248 (emphasis in original).

In his Second Entitlement Ruling, although the previous special master again ruled for Petitioner, he did not consider Langer-Gould in his analysis, noting that the Court's "explicit findings regarding the Langer-Gould study … preclude it from further consideration." Second Entitlement Ruling at *25.

"The law of the case is a judicially created doctrine, the purposes of which are to prevent the relitigation of issues that have been decided and to ensure that trial courts follow the decisions of appellate courts." *See Gould, Inc. v. United States*, 67 F.3d 925, 927–28 (Fed. Cir. 1995) (citing *Jamesbury Corp. v. Litton Indus. Prods., Inc.*, 839 F.2d 1544, 1550 (Fed. Cir. 1988), *cert. denied*, 488 U.S. 828, 109 S.Ct. 80, 102 L.Ed.2d 57 (1988), *overruled on other grounds by, A.C. v. Aukerman Co. v. R.L. Chaides Constr. Co.*, 960 F.2d 1020 (Fed. Cir. 1992). The law of the case doctrine applies in Vaccine Act cases. *Suel v. Sec'y of Health & Hum. Servs.*, 192 F.3d 981 (Fed. Cir. 1999).

In *Doles II*, the Court remanded the case to the Office of Special Masters and directed that a new special master "consider the record anew." *Doles II* at 733. I asked the parties to discuss this issue at oral argument -- specifically whether the direction to consider the record anew meant that I should consider the entire record including the Langer-Gould study, or whether I should consider the record without reference to Langer-Gould. Both parties agreed that I am precluded from considering Langer-Gould's findings -- that vaccination in people younger than 50 was associated with an increased risk of CNS ADS within 30 days after vaccination -- as support for the current case. ECF No. 128 at 7-8, 23. Because the parties are in agreement, I have not considered the study in my analysis of *Loving* prong four.[11]

[11] Petitioner contends that although I am precluded from considering the results of Langer-Gould, I still am permitted to consider "interpretative statements" by the authors which "explain[] and discuss[] these findings and consider[] their implications." ECF No. 128 at 7. As an example, Petitioner says that I may consider the statement "Vaccines may accelerate the transition from subclinical to overt autoimmunity in patients with preexisting disease." *Id.* at 11. However, the Court opined in *Doles I* that "[a] finding of causation would have to be *despite* the Langer-Gould study, not *because* of it" *Doles I* at 248 (emphasis in original). Because of this, I find that any consideration of Langer-Gould would be improper, based on the plain language in *Doles I*.

C. Significant Aggravation of MS

MS is an autoimmune disease that causes demyelination of the central nervous system. MS lesions can appear as enhancing or non-enhancing on MRI. Before a patient has an MRI with contrast, they are injected intravenously with a contrast dye called gadolinium. In a healthy person, or in an MS patient not having a flare, that dye should remain in the bloodstream. However, if an MS patient is symptomatic, the gadolinium will leak into the brain or spinal cord through an opening in the blood-brain barrier and will show as an enhancing image on MRI. Thus gadolinium enhancement signifies that a lesion is active.

MS is characterized by lesions that are disseminated in space and time. Dissemination in space is shown when one or more lesions exist in two or more of four parts of the CNS (in this case, periventricular and spinal cord). Thompson et al., *Diagnosis of Multiple Sclerosis: 2017 Revisions of the McDonald Criteria*, 17 LANCET NEUROLOGY 162, 168 (2018) (filed as Ex. C) (hereinafter "McDonald Criteria"). Dissemination in time can be demonstrated by the "simultaneous presence of gadolinium-enhancing and non-enhancing lesions." McDonald Criteria at 168 (panel 5). MS's first clinically apparent neurological event is described as clinically isolated syndrome (CIS). First Sriram Rep. at 7. Both experts agree that Petitioner has MS.

Dr. Steel's opinion, contained in his two expert reports, has been the subject of much discussion and disagreement. As outlined below, although Dr. Steel's opinion is less than clear, I do find that he has articulated a theory fairly and appropriately analyzed as significant aggravation.

In his first expert report, Dr. Steel opined that Petitioner experienced an attack of focal myelitis. First Steel Rep. at 3. After this attack, she met the current diagnostic criteria for MS due to the existence of old lesions in the brain that did not cause clinical symptoms. *Id.* Dr. Steel opined that the "vaccinations likely did not cause the MS but rather unmasked it, i.e. caused it to become clinically significant during her medical evaluation." *Id.* He further stated that this initial event was a "Clinically Isolated Event" which was Petitioner's "first episode of neurological symptoms typical of an MS relapse in a person not known to have MS." *Id.* A clinically isolated event, or clinically isolated syndrome is a term of art related to MS. "In a patient later diagnosed with MS, the clinically isolated syndrome constitutes the first attack of the disease." First Sriram Rep. at 7.

If the report had stopped here, it would have clearly articulated that Petitioner had clinically silent MS, and that her underlying disease was "unmasked" by the vaccinations, manifesting in her first clinical episode.

However, Dr. Steel went on in this first report to describe Petitioner's condition as an attack of myelitis in the context of underlying disease. First Steel Rep. at 5. He equated her clinically silent MS with an "undiagnosed susceptibility." *Id.* This verbiage lends some support to the position that Dr. Steel has advanced a theory that the attack of spinal myelitis was an event separate and distinct from Petitioner's MS.

Dr. Steel's second report further muddies the waters. He stated the following:

> [Petitioner] had clinically silent MS that came to light after her attack of TM but her MS is a red herring and has served to confuse the issue. In my report of 21 May 2019 I made no assertion of a causal relationship between the vaccines and MS. I gave a limited and carefully worded opinion regarding the myelitis only. Dr. Sriram's rebuttal of 22 November 2019 focused on MS but did not address the actual causal relationship that I have asserted, between [Petitioner's] April 2016 vaccinations and her subsequent attack of spinal myelitis. By discussing MS only, he failed to address our central point.

Second Steel Rep. at 1-2. Respondent contends that in labeling MS as a "red herring", Dr. Steel cannot be positing that the vaccines Petitioner received caused the significant aggravation of her MS. ECF No. 128 at 28 (arguing that "I think that when he says that MS is a red herring, I take that very seriously and very literally at his word…. I trust that if he had a significant aggravation opinion, he would have said so.").

Dr. Steel clarified this comment later in his second report. He noted that "Dr. Sriram's extensive discussion of the epidemiology of vaccinations and MS does not address my claim that the vaccine triggered an episode of spinal myelitis in the context of the patient's pre-existing clinically silent MS." Second Steel Rep. at 7. In labeling MS as a red herring, it appears that Dr. Steel attempted to distinguish this case from other (sometimes unsuccessful) program cases alleging vaccine-induced MS by describing Petitioner's clinical course as involving a discrete event that he alternatively called myelitis, TM, CIS, and APTM. Dr. Steel alleged that Petitioner's vaccination was the cause of this isolated event, which based on the MRI evidence, constituted Petitioner's first clinical event, but not the beginning of her disease.

In examining the totality of the language contained in Dr. Steel's expert reports, I conclude that he has articulated a theory of significant aggravation. In particular, the use of the term "unmasked" (which Dr. Steel used in his first and second expert reports) effectively describes a significant aggravation. Unmasked means "to reveal the true nature of" something.[12] In this case, Dr. Steel contended that the vaccines revealed the true nature of Petitioner's condition: pre-existing, clinically-silent MS that became active after vaccination. Further, Dr. Steel's use of the term "Clinically Isolated Event" to describe Petitioner's condition also suggests that he considered her June 2016 event to be a discrete occurrence in her MS disease course.

In most cases, there is a distinction between the cause of an event and that event's significant aggravation. That normal, clear-cut distinction is blurred in the case at bar.

Both experts agree that Petitioner's correct diagnosis is MS, and further, that the initial clinical appearance of her disease evidenced dissemination in both space and time. First Steel Rep. at 3; First Sriram Rep. at 7-8. Accordingly, Petitioner's episode of CIS that she experienced in June of 2016 qualified her for an MS diagnosis because she had non-enhancing lesions in the brain (described by Dr. Steel as "likely preexistent, likely old, and clinically silent." Second Steel Rep. at 6) and an enhancing lesion in the cervical spine at C3-C4. Ex. 2 at 39-41; Ex. 4 at 70-71, 76. Accordingly, when Dr. Steel opined that Petitioner's CIS was caused by her vaccination, in the

[12] www.merriam-webster.com/dictionary/unmasked (last accessed, Feb. 22, 2023).

context of this case, that also meant that her pre-existing but clinically silent MS had been significantly aggravated.

I also note Respondent conceded that Petitioner has met *Loving* prongs one through three. ("Respondent agrees that under *Sharpe*, petitioner suffered a "significant aggravation" of her condition, insofar as her condition following her vaccinations was worse than before and resulted in "markedly greater disability." 42 U.S.C. § 300aa-33(4). Accordingly, respondent does not address *Loving* prongs one through three in this response." ECF No. 98 at 7, fn 3). This means whether the case is analyzed as a causation in fact or a significant aggravation, only *Althen* prongs one through three/*Loving* prongs four through six need be examined.

Based on the above, I find that Dr. Steel has presented a significant aggravation theory in his expert reports, and accordingly, that it is appropriate to analyze this case pursuant to *Loving v. Secretary of Health and Human Services*.

V. Applicable Law

A. Petitioner's Burden in Vaccine Program Cases

Under the Vaccine Act, when a petitioner suffers an alleged injury that is not listed in the Vaccine Injury Table, a petitioner may demonstrate that he suffered an "off-Table" injury. § 11(c)(1)(C)(ii).

In attempting to establish entitlement to a Vaccine Program award of compensation for a off-Table claim, a petitioner must satisfy all three of the elements established by the Federal Circuit in *Althen v. Sec'y of Health & Hum. Servs.*, 418 F.3d 1274 (Fed. Cir. 2005). *Althen* requires that petitioner establish by preponderant evidence that the vaccination he received caused his injury "by providing: (1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of a proximate temporal relationship between vaccination and injury." *Id.* at 1278.

Under the first prong of *Althen*, petitioners must provide a "reputable medical theory," demonstrating that the vaccine received *can cause* the type of injury alleged. *Pafford*, 451 F.3d at 1355-56 (citations omitted). To satisfy this prong, a petitioner's theory must be based on a "sound and reliable medical or scientific explanation." *Knudsen v. Sec'y of Health & Hum. Servs*., 35 F.3d 543, 548 (Fed. Cir. 1994). Proof that the proffered medical theory is reasonable, plausible, or possible does not satisfy a petitioner's burden. *Boatmon v. Sec'y of Health & Hum. Servs*., 941 F.3d 1351, 1359-60 (Fed. Cir. Nov. 7, 2019).

Petitioners may satisfy the first *Althen* prong without resort to medical literature, epidemiological studies, demonstration of a specific mechanism, or a generally accepted medical theory. *Andreu v. Sec'y of Health & Hum. Servs.*, 569 F.3d 1367, 1378-79 (Fed. Cir. 2009) (citing *Capizzano v. Sec'y of Health & Hum. Servs.*, 440 F.3d 1317, 1325-26 (Fed. Cir. 2006). However, special masters are "entitled to require some indicia of reliability to support the assertion of the expert witness." *Boatmon*, 941 F.3d at 1360, *quoting Moberly v. Sec'y of Health & Hum. Servs.*, 592 F.3d 1315, 1324 (Fed. Cir. 2010). Special Masters, despite their expertise, are not empowered

by statute to conclusively resolve what are complex scientific and medical questions, and thus scientific evidence offered to establish *Althen* prong one is viewed "not through the lens of the laboratorian, but instead from the vantage point of the Vaccine Act's preponderant evidence standard." *Id.* at 1380. Accordingly, special masters must take care not to increase the burden placed on petitioners in offering a scientific theory linking vaccine to injury. *Contreras v. Sec'y of Health & Hum. Servs*., 121 Fed. Cl. 230, 245 (2015), *vacated on other grounds*, 844 F.3d 1363 (Fed. Cir. 2017); *see also Hock v. Sec'y of Health & Hum. Servs*., No. 17-168V, 2020 U.S. Claims LEXIS 2202 at *52 (Fed. Cl. Spec. Mstr. Sept. 30, 2020).

The second *Althen* prong requires proof of a logical sequence of cause and effect, usually supported by facts derived from a petitioner's medical records. *Althen*, 418 F.3d at 1278; *Andreu*, 569 F.3d at 1375-77; *Capizzano*, 440 F.3d at 1326 ("medical records and medical opinion testimony are favored in vaccine cases, as treating physicians are likely to be in the best position to determine whether a 'logical sequence of cause-and-effect show[s] that the vaccination was the reason for the injury'") (quoting *Althen*, 418 F.3d at 1280). Medical records are generally viewed as particularly trustworthy evidence, since they are created contemporaneously with the treatment of the patient. *Cucuras v. Sec'y of Health & Hum. Servs.*, 993 F.2d 1525, 1528 (Fed. Cir. 1993).

However, medical records and/or statements of a treating physician's views do not *per se* bind the special master to adopt the conclusions of such an individual, even if they must be considered and carefully evaluated. Section 13(b)(1) (providing that "[a]ny such diagnosis, conclusion, judgment, test result, report, or summary shall not be binding on the special master or court"). As with expert testimony offered to establish a theory of causation, the opinions or diagnoses of treating physicians are only as trustworthy as the reasonableness of their suppositions or bases. The views of treating physicians should also be weighed against other, contrary evidence also present in the record. *Hibbard v. Sec'y of Health & Hum. Servs*., 100 Fed. Cl. 742, 749 (2011), *aff'd*, 698 F.3d 1355 (Fed. Cir. 2012); *Caves v. Sec'y of Health & Hum. Servs*., No. 06-522V, 2011 WL 1935813, at *17 (Fed. Cl. Spec. Mstr. Apr. 29, 2011), *mot. for review den'd*, 100 Fed. Cl. 344, 356 (2011), *aff'd without opinion*, 475 Fed.App'x 765 (Fed. Cir. 2012).

The third *Althen* prong requires establishing a "proximate temporal relationship" between the vaccination and the injury alleged. *Althen*, 418 F.3d at 1281. That term has been equated to the phrase "medically-acceptable temporal relationship." *Id.* A petitioner must offer "preponderant proof that the onset of symptoms occurred within a timeframe which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation." *de Bazan v. Sec'y of Health & Hum. Servs*., 539 F.3d 1347, 1352 (Fed. Cir. 2008). The explanation for what is a medically acceptable timeframe must also coincide with the theory of how the relevant vaccine can cause an injury (*Althen* prong one's requirement). *Id.* at 1352; *Shapiro v. Sec'y of Health & Hum. Servs*., 101 Fed. Cl. 532, 542 (2011), *recons. den'd after remand*, 105 Fed. Cl. 353 (2012), *aff'd mem*., 503 F. App'x 952 (Fed. Cir. 2013); *Koehn v. Sec'y of Health & Hum. Servs*., No. 11-355V, 2013 WL 3214877 (Fed. Cl. Spec. Mstr. May 30, 2013), *mot. for review den'd* (Fed. Cl. Dec. 3, 2013), *aff'd*, 773 F.3d 1239 (Fed. Cir. 2014).

The Vaccine Act defines significant aggravation as "any change for the worse in a preexisting condition which results in markedly greater disability, pain, or illness accompanied by substantial deterioration of health." § 300aa-33(4). In *Loving*, the United States Court of Federal

Claims established the governing six-part test for off-Table significant aggravations. Petitioner must prove by a preponderance of the evidence:

> (1) The person's condition prior to administration of the vaccine, (2) the person's current condition (or the condition following the vaccination if that is also pertinent), (3) whether the person's current condition constitutes a 'significant aggravation' of the person's condition prior to vaccination, (4) a medical theory causally connecting such a significant worsened condition to the vaccination, (5) a logical sequence of cause and effect showing that the vaccination was the reason for the significant aggravation, and (6) a showing of a proximate temporal relationship between the vaccination and the significant aggravation.

Loving v. Sec'y of Health & Hum. Servs., 86 Fed. Cl. 135, 144 (2009); *see also W.C. v. Sec'y of Health & Human Servs.*, 704 F.3d 1352, 1357 (Fed. Cir. 2013) (adopting this as the proper legal standard for significant aggravation claims brought under the Vaccine Act). *Loving* prongs four, five, and six are derived from the Federal Circuit's test for off-Table actual causation cases. *Althen v. Sec'y of Health & Hum. Servs.*, 17 F.3d 374 (Fed. Cir. 1994).

In *Sharpe,* the Federal Circuit clarified the *Loving* prongs and what is required by petitioners to successfully demonstrate a causation-in-fact significant aggravation claim. *Sharpe v. Sec'y of Health & Hum. Servs.,* 964 F.3d 1072 (Fed. Cir. 2020). *Loving* prong three only requires a comparison of a petitioner's current, post-vaccination condition with his pre-existing pre-vaccination condition. *Sharpe* at 1082; *Whitecotton v. Sec'y of Health & Hum. Servs.,* 81 F.3d 1099 (Fed. Cir. 1996). A petitioner is not required to demonstrate an expected outcome or that his post-vaccination condition was worse than such an expected outcome. *Sharpe* at 1081. Further, a petitioner is not required "to disprove that a pre-existing genetic mutation caused [his] significant aggravation." *Sharpe* at 1087.

Under *Loving* prong four, a petitioner need only provide a "medical theory causally connecting [petitioner's] significantly worsened condition to the vaccination." *Sharpe* at 1083; *see also Loving*, 86 Fed. Cl. at 144. In other words, a petitioner is required to present a medically reliable theory demonstrating that a vaccine "can cause a significant worsening" of the condition. *Sharpe* at 1083 (citing to *Pafford ex. rel. Pafford v. Sec'y of Health & Hum. Servs.,* 451 F.3d 1352, 1356-57 (Fed. Cir. 2006). A petitioner may be able to establish a prima facie case under *Loving* prong four without eliminating a pre-existing condition as the cause of her significantly aggravated injury. *Id.*; citing *Walther v. Sec'y of Health & Hum. Servs.,* 485 F. 3d 1146, 1151 (Fed. Cir. 2007) (noting that "the government bears the burden of establishing alterative causation. . . . once petitioner has established a prima facie case").

Loving prong five requires a petitioner to show "a logical sequence of cause and effect showing that the vaccination was the reason for the significant aggravation." *Loving,* 86 Fed. Cl. at 144. In other words, a petitioner must show that the vaccinations "did" cause a worsening of petitioner's underlying disorder. *Id.*

In determining whether a petitioner is entitled to compensation, a special master must consider the entire record and is not bound by any particular piece of evidence. § 13(b)(1) (stating

that a special master is not bound by any "diagnosis, conclusion, judgment, test result, report, or summary" contained in the record). Furthermore, a petitioner is not required to present medical literature or epidemiological evidence to establish any *Althen* prong. The special master essentially must weigh and evaluate opposing evidence in deciding whether a petitioner has met their burden of proof. *Andreu v. Sec'y of Health & Hum. Servs.*, 569 F.3d 1367, 1380 (Fed. Cir. 2009); *see also Grant v. Sec'y of Health & Hum. Servs.*, 956 F.2d 1144, 1149 (Fed. Cir. 1992).

B. Law Governing Analysis of Fact Evidence

The process for making factual determinations in Vaccine Program cases begins with analyzing the medical records, which are required to be filed with the petition. Section 11(c)(2). The special master is required to consider "all [] relevant medical and scientific evidence contained in the record," including "any diagnosis, conclusion, medical judgment, or autopsy or coroner's report which is contained in the record regarding the nature, causation, and aggravation of the petitioner's illness, disability, injury, condition, or death," as well as the "results of any diagnostic or evaluative test which are contained in the record and the summaries and conclusions." Section 13(b)(1)(A). The special master is then required to weigh the evidence presented, including contemporaneous medical records and testimony. *See Burns v. Sec'y of Health & Hum. Servs.*, 3 F.3d 413, 417 (Fed. Cir. 1993) (it is within the special master's discretion to determine whether to afford greater weight to contemporaneous medical records than to other evidence, such as oral testimony surrounding the events in question that was given at a later date, provided that such determination is evidenced by a rational determination).

Medical records created contemporaneously with the events they describe are generally trustworthy because they "contain information supplied to or by health professionals to facilitate diagnosis and treatment of medical conditions," where "accuracy has an extra premium." *Kirby v. Sec'y of Health & Hum. Servs.*, 997 F.3d 1378 (Fed. Cir. 2021) citing *Cucuras*, 993 F.2d at 1528. This presumption is based on the linked proposition that (i) sick people visit medical professionals; (ii) sick people honestly report their health problems to those professionals; and (iii) medical professionals record what they are told or observe when examining their patients in as accurate a manner as possible, so that they are aware of enough relevant facts to make appropriate treatment decisions. *Sanchez v. Sec'y of Health & Hum. Servs.*, No. 11-685V, 2013 WL 1880825 at *2 (Fed. Cl. Spec. Mstr. Apr. 10, 2013) *mot. for rev. denied*, 142 Fed. Cl. 247, 251-52 (2019), *vacated on other grounds and remanded*, 809 Fed. App'x 843 (Fed. Cir. 2020).

Accordingly, if the medical records are clear, consistent, and complete, then they should be afforded substantial weight. *Lowrie v. Sec'y of Health & Hum. Servs.*, No. 03-1585V, 2005 WL 6117475 at *20 (Fed. Cl. Spec. Mstr. Dec. 12, 2005). Indeed, contemporaneous medical records are generally found to be deserving of greater evidentiary weight than oral testimony -- especially where such testimony conflicts with the record evidence. *Cucuras*, 993 F.2d at 1528; see also *Murphy v. Sec'y of Health & Hum. Servs.*, 23 Cl. Ct. 726, 733 (1991), *aff'd per curiam*, 968 F.2d 1226 (Fed. Cir. 1992), *cert. den'd*, *Murphy v. Sullivan*, 506 U.S. 974 (1992) (citing *United States*

v. U.S. Gypsum Co., 333 U.S. 364, 396 (1947) ("[i]t has generally been held that oral testimony which is in conflict with contemporaneous documents is entitled to little evidentiary weight.")).

However, there are situations in which compelling oral testimony may be more persuasive than written records, such as where records are deemed to be incomplete or inaccurate. *Campbell v. Sec'y of Health & Hum. Servs.*, 69 Fed. Cl. 775, 779 (2006) ("like any norm based upon common sense and experience, this rule should not be treated as an absolute and must yield where the factual predicates for its application are weak or lacking"); *Lowrie*, 2005 WL 6117475 at *19 ("[w]ritten records which are, themselves, inconsistent, should be accorded less deference than those which are internally consistent") (quoting *Murphy*, 23 Cl. Ct. at 733)). Ultimately, a determination regarding a witness's credibility is needed when determining the weight that such testimony should be afforded. *Andreu*, 569 F.3d at 1379; *Bradley v. Sec'y of Health & Hum. Servs.*, 991 F.2d 1570, 1575 (Fed. Cir. 1993).

When witness testimony is offered to overcome the presumption of accuracy afforded to contemporaneous medical records, such testimony must be "consistent, clear, cogent and compelling." *Sanchez*, 2013 WL 1880825 at *3 (citing *Blutstein v. Sec'y of Health & Hum. Servs.*, No. 90-2808V, 1998 WL 408611 at *5 (Fed. Cl. Spec. Mstr. June 30, 1998)). In determining the accuracy and completeness of medical records, the Court of Federal Claims has listed four possible explanations for inconsistencies between contemporaneously created medical records and later testimony: (1) a person's failure to recount to the medical professional everything that happened during the relevant time period; (2) the medical professional's failure to document everything reported to her or him; (3) a person's faulty recollection of the events when presenting testimony; or (4) a person's purposeful recounting of symptoms that did not exist. *LaLonde v. Sec'y of Health & Hum. Servs.*, 110 Fed. Cl. 184, 203-04 (2013), *aff'd*, 746 F.3d 1334 (Fed. Cir. 2014). In making a determination regarding whether to afford greater weight to contemporaneous medical records or other evidence, such as testimony at hearing, there must be evidence that this decision was the result of a rational determination. *Burns*, 3 F.3d at 417.

C. Analysis of Expert Testimony

Establishing a sound and reliable medical theory connecting the vaccine to the injury often requires petitioners to present expert testimony in support of their claim. *Lampe v. Sec'y of Health & Hum. Servs.*, 219 F.3d 1357, 1361 (Fed. Cir. 2000). Vaccine Program expert testimony is usually evaluated according to the factors for analyzing scientific reliability set forth in *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579, 594-96 (1993). *See Cedillo v. Sec'y of Health & Hum. Servs.*, 617 F.3d 1328, 1339 (Fed. Cir. 2010) (*citing Terran v. Sec'y of Health & Hum. Servs.*, 195 F.3d 1302, 1316 (Fed. Cir. 1999). "The *Daubert* factors for analyzing the reliability of testimony are: (1) whether a theory or technique can be (and has been) tested; (2) whether the theory or technique has been subjected to peer review and publication; (3) whether there is a known or potential rate of error and whether there are standards for controlling the error; and (4) whether the theory or technique enjoys general acceptance within a relevant scientific community." *Terran*, 195 F.3d at 1316 n.2 (citing *Daubert*, 509 U.S. at 592-95).

The *Daubert* factors play a slightly different role in Vaccine Program cases than they do when applied in other federal judicial fora. *Daubert* factors are employed by judges to exclude

evidence that is unreliable and potentially confusing to a jury. In Vaccine Program cases, these factors are used in the weighing of the reliability of scientific evidence. *Davis v. Sec'y of Health & Hum. Servs.*, 94 Fed. Cl. 53, 66-67 (2010) ("uniquely in this Circuit, the *Daubert* factors have been employed also as an acceptable evidentiary-gauging tool with respect to persuasiveness of expert testimony already admitted").

Respondent frequently offers one or more experts of his own in order to rebut petitioners' case. Where both sides offer expert testimony, a special master's decision may be "based on the credibility of the experts and the relative persuasiveness of their competing theories." *Broekelschen v. Sec'y of Health & Hum. Servs.*, 618 F.3d 1339, 1347 (Fed. Cir. 2010) (citing *Lampe*, 219 F.3d at 1362). However, nothing requires the acceptance of an expert's conclusion "connected to existing data only by the *ipse dixit* of the expert," especially if "there is simply too great an analytical gap between the data and the opinion proffered." *Snyder*, 88 Fed. Cl. at 743 (quoting *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997)). A "special master is entitled to require some indicia of reliability to support the assertion of the expert witness." *Moberly*, 592 F.3d at 1324. Weighing the relative persuasiveness of competing expert testimony, based on a particular expert's credibility, is part of the overall reliability analysis to which special masters must subject expert testimony in Vaccine Program cases. *Id.* at 1325-26 ("[a]ssessments as to the reliability of expert testimony often turn on credibility determinations").

D. Consideration of Medical Literature

Although this decision discusses some but not all of the medical literature in detail, I reviewed and considered all of the medical records and literature submitted in this matter. *See Moriarty v. Sec'y of Health & Hum. Servs.*, 844 F.3d 1322, 1328 (Fed. Cir. 2016) ("We generally presume that a special master considered the relevant record evidence even though [s]he does not explicitly reference such evidence in h[er] decision."); *Simanski v. Sec'y of Health & Hum. Servs.*, 115 Fed. Cl. 407, 436 (2014) ("[A] Special Master is 'not required to discuss every piece of evidence or testimony in her decision.'" (citation omitted)), *aff'd*, 601 F. App'x 982 (Fed. Cir. 2015).

VI. Analysis

A. *Loving* Prongs One through Three

Respondent conceded that Petitioner has met *Loving* prongs one through three. ECF No. 98 at 7, fn 3. I find these elements of Petitioner's case have been satisfied.

B. *Loving* Prong Four/*Althen* Prong One

In the context of the Program, "to establish causation, the standard of proof is preponderance of evidence, not scientific certainty." *Langland v. Sec'y of Health & Hum. Servs.*, 109 Fed. Cl. 421, 441 (Fed Cir. 2013). Under *Loving* prong four/*Althen* prong one, the causation theory must relate to the injury alleged. Thus, Petitioner must provide a "reputable" medical or scientific explanation, demonstrating that the vaccines received can cause a significant aggravation of the type of injury alleged. *Pafford ex rel. Pafford v. Sec'y of Health & Hum. Servs.*, 451 F.3d

1352, 1355-56 (Fed. Cir. 2006). The theory must be based on a "sound and reliable medical or scientific explanation." *Knudsen v. Sec'y of Health & Hum. Servs.*, 35 F.3d 543, 548 (Fed. Cir. 1994). It must only be "legally probable, not medically or scientifically certain." *Id*. at 549.

Petitioner provided several items of medical literature to support her theory that the Tdap and/or polio vaccines can cause a significant aggravation of MS. While Petitioner presented some reliable proof in support of her theory, I find that overall, it was insufficient to meet her burden. I have discussed the relevant medical literature below.

1. Fujinami et al.

Dr. Steel relied on medical literature by Fujinami and colleagues that posits a relationship between an initial viral infection and later autoimmune disease. First Steel Rep. at 4-5 (citing Fujinami et al., *Molecular mimicry, bystander activation, or viral persistence: Infections and autoimmune disease*, 19 CLIN. MICROBIOLOGY REV. 80-94 (2006) (filed as Ex. 24) (hereinafter "Fujinami"). Fujinami contends that the ways in which a virus and a host's body interact during an infection "set the stage for a 'fertile field' where the host and/or target organ is 'primed' for subsequent immunopathology." *Id.* at 80. In other words, a viral infection can make the later development of autoimmunity more likely by priming the host's immune system to become overactive upon subsequent challenge, resulting in disease. *Id.*

Fujinami argues that, while the etiology of MS is not known, epidemiological and laboratory data point to autoimmunity. Fujinami at 84. In the study, Fujinami tested the fertile field theory by infecting mice with an engineered virus that shared epitopes with myelin-associated glycoprotein. *Id.* Once the viral infection cleared, the mice were injected with complete Freund's adjuvant to trigger an immune response. *Id.* Eighty to 90% of the mice developed demyelinating lesions. *Id.* Fujinami opines that this supports the fertile field theory of post-infection autoimmunity as a trigger for MS. *Id.*

Fujinami contends that an initial virus primes autoreactive T cells. Subsequently "later events may trigger these cells to cause disease." Fujinami at 83. However, the later events cited by the authors were some wild viruses and adjuvant. Fujinami did not discuss vaccines as having a causative role in MS exacerbations or in any other disease. Certainly, the Fujinami paper is not inconsistent with Petitioner's causation theory, it is just not sufficient, without more, for Petitioner to meet her burden. Petitioner's additional evidence, however, does not bridge this analytical gap.

2. Frohman & Wingerchuk

Petitioner filed an article from Frohman & Wingerchuk which discusses transverse myelitis. These authors note "the transverse myelitis syndrome may arise from various causes, but it most often occurs as an autoimmune phenomenon after an infection or vaccination (accounting for 60% of the cases in children) or as a result of a direct infection, an underlying systemic autoimmune disease, or an acquired demyelinating disease such as multiple sclerosis…" Frohman & Wingerchuk at 564.

Figure 1 of the Frohman & Wingerchuk article is a flow chart which states that findings of demyelination on brain MRI, along with oligoclonal bands or increased IgG index in the CSF, and abnormal visual evoked response should lead to the conclusion that the patient is at a high risk of MS as opposed to TM. Frohman & Wingerchuk at 566. In addition, this flow chart limits post-vaccination TM to longitudinally extensive TM, as opposed to the partial myelitis that Petitioner experienced. *Id.* Partial TM on the other hand, is strongly associated with MS. *Id.* The authors note that "[t]he presence on MRI of brain lesions that are characteristic of demyelination indicates a high risk of multiple sclerosis after partial myelitis event." *Id.* at 567. This is consistent with Dr. Sriram's opinion that "[t]he clinical picture of incomplete transverse myelitis is the most common feature of the myelitic syndrome of MS and fits the clinical finding seen in Ms. Doles." First Sriram Rep. at 1.

However, the authors also indicate that disease-associated TM can still be caused by vaccination: "the occurrence of transverse myelitis after infection or vaccination does not preclude further evaluation, since infection or immunization may also trigger attacks of myelitis in the context of underlying disease (especially multiple sclerosis or neuromyelitis optica)." Frohman & Wingerchuk at 567. Dr. Sriram disputes this statement. He states "there is no citation to support the paper's claim that vaccination can cause transverse myelitis in a patient with underlying MS. In the 10 years since this paper was published there has also been no evidence that vaccines can aggravate myelitis or any other acute inflammatory demyelinating syndrome." Second Sriram Rep. at 4.

Frohman & Wingerchuk's flow chart demonstrates that post-vaccination TM is longitudinally extensive, which is different from the partial myelitis that Petitioner experienced. This conclusion is seemingly contradicted by the sentence which notes that vaccination can trigger myelitis in the context of underlying MS. It is difficult to further elucidate this issue on the existing record. Ultimately, this sentence from Frohman & Wingerchuk ("the occurrence of transverse myelitis after infection or vaccination does not preclude the need for further evaluation, since infection or immunization may also trigger attacks of myelitis in the context of underlying disease (especially multiple sclerosis or neuromyelitis optica)") does provide some support for Petitioner's position. Frohman & Wingerchuk at 567.

3. Case Reports

In his expert reports, Dr. Steel relies on multiple case reports from review literature exploring possible connections between various vaccinations and a variety of CNS demyelinating conditions. It is well established in the Vaccine Program that while case reports can constitute evidence in favor of causation, their evidentiary heft is significantly less than that of epidemiological literature because they "can by their nature only present indicia of causation." *Campbell v. Sec'y of Health & Hum. Servs.*, 97 Fed. Cl. 650, 668 (2011). Special masters have discussed the evidentiary value of case reports in prior Vaccine Program decisions. *See, e.g., Loyd, next Friend of CL v. Sec'y of Health & Hum. Servs.*, No. 16-811V, 2021 WL 2708941 (Fed. Cl. Spec. Mstr. May 20, 2021) (describing case reports as a "category of evidence inherently given less weight in the Program, especially when contrasted with on-point and reliable epidemiologic proof"); *Pearson v. Sec'y of Health & Hum. Servs.*, No. 17-489V, 2019 WL 1150044, at *11 (Fed. Cl. Spec. Mstr. Feb. 7, 2019) (concluding that case reports receive only limited evidentiary

weight and cannot cure *Althen* prong one deficiencies); *see also Harris v. Sec'y of Health & Hum. Servs.*, No. 10-322V, 2014 WL 3159377, at *18 (Fed. Cl. Spec. Mstr. June 10, 2014) (noting that "case reports are generally not a valuable form of evidence").

None of the case reports cited by Petitioner establish a link between the polio or Tdap vaccines and clinical worsening of MS. *See, e.g.,* Cabrera-Maqueda et al., *Optic neuritis in pregnancy after Tdap vaccination: Report of two cases*, 160 CLINICAL NEUROSURGERY 116-18 (2017) (filed as Ex. 35) (describing two cases of optic neuritis in pregnant women who received Tdap vaccinations); Agmon-Levin et al., *Transverse myelitis and vaccines: a multi-analysis*, 18 LUPUS 1198-1204 (2009) (filed as Ex. 42) (hereinafter "Agmon-Levin") (finding five cases of transverse myelitis after diphtheria-tetanus or diphtheria-tetanus-pertussis vaccination reported between 1970 and 2009); Karussis & Petrou (identifying 71 cases of post-vaccination inflammatory CNS disease reported between 1979 and 2013, of which one was a case of MS after HPV vaccination). Although Karussis & Petrou note that vaccinations "have [] been linked to the occurrence of relapses in MS," they cite as support for this contention a review article associating MS relapses with the yellow fever vaccine. Ex. 36 at 220 (citing Loebermann et al., *Vaccination against infection in patients with multiple sclerosis*, 8 NATURE REVIEWS: NEUROLOGY 143-51 (2012) (filed as Ex. 28)). These reports showcase the rarity of post-vaccination inflammatory CNS disease, particularly in the context of the enormous number of vaccine doses administered. Petitioner asks the Court to infer that the Tdap vaccine can significantly aggravate MS based on a small number of anecdotal reports of several different conditions that developed after a wide variety of vaccinations.

The attenuation of the connection between CNS demyelinating disease and vaccines in these case reports combined with the relatively low evidentiary value of case reports generally leads me to conclude that this evidence does very little to advance Petitioner's *Loving* prong four causation theory.

4. Other Literature

Dr. Steel cites a review article discussing epidemiological literature on potential links between (1) the hepatitis B and HPV vaccines and MS, and (2) the H1N1 flu vaccine and narcolepsy. Nguyen et al., *Vaccine-associated inflammatory diseases of the central nervous system: from signals to causation*, 29 CURRENT OPINION: NEUROLOGY 362-71 (2016) (filed as Ex. 63). This article provides no persuasive support for Petitioner's arguments. The literature reviewed does not support an increased risk of MS or aggravation of MS associated with the hepatitis B or HPV vaccines. *Id*. at 364-66. Finding some evidence for a causal connection between the Pandemrix H1N1 vaccine and narcolepsy, but no such link between other formulations of the H1N1 vaccine, the reviewers suggest that the AS03 adjuvant used in Pandemrix may be to blame. *Id.* at 368. Again, this does not lend support to Petitioner's theory because the Tdap vaccine she received is adjuvanted with aluminum hydroxide and the polio vaccine she received does not contain an adjuvant. Boostrix Package Insert (filed as Ex. 59) at 16; *see* IPOL Package Insert.[13]

[13] Petitioner did not file the package insert for the inactivated polio vaccine, but it is publicly available here: www.fda.gov/files/vaccines%2C%20blood%20%26%20biologics/published/Package-Insert-IPOL.pdf (last accessed March 9, 2023).

Finally, Dr. Steel cites the 2012 finding by the Institute of Medicine ("IOM") that there is insufficient evidence at present to accept or reject a causal relationship between the Tdap vaccine and MS relapse in adults. Institute of Medicine, *Adverse Effects of Vaccines: Evidence and Causality*, NAT'L ACAD. SCI. 1, 71 (2012) (filed as Ex. 66). While it is true that the IOM declined to say that the causal relationship that Petitioner asserts is impossible, the lack of affirmative evidence in the literature review renders this statement less than compelling in the context of Petitioner's burden under prong four.

5. Evidence Presented by Respondent

The record also contains evidence weighing against Petitioner's argument that the vaccines she received can significantly aggravate MS. Drs. Steel and Sriram cited a case-crossover study of European MS patients that found "no increase in the specific risk of relapse associated with tetanus, hepatitis B, or influenza vaccination." Confavreux et al., *Vaccinations and the risk of relapse in multiple sclerosis*, 344 NEW ENG. J. OF MED. 319-26 (2001) (filed as Exs. 27, O). Dr. Sriram also cited a literature review finding no increased risk of developing MS after hepatitis B, HPV, flu, MMR, variola, tetanus, bacillus Calmette-Guérin, polio, or diphtheria vaccination. Mailand & Frederiksen at 1035.

Furthermore, multiple studies cited by Dr. Sriram associate certain vaccines with a decreased risk of developing MS. *See, e.g.*, Mailand & Frederiksen at 1046 (finding a decreased risk of MS onset after tetanus vaccination); Farez & Correale at 1197 (finding a decreased risk of MS onset after tetanus and diphtheria vaccination); Hernan et al., *Tetanus vaccination and risk of multiple sclerosis*, 67 NEUROLOGY 212-15, 214 (2006) (filed as Ex. K) (finding a decreased risk of MS onset after tetanus vaccination).

As Dr. Sriram noted in summarizing Respondent's medical literature, "MS patients are a highly studied population. Large scale studies have looked for an increase of MS exacerbations following vaccinations, and no association has been found." First Sriram Rep. at 10. Epidemiologic evidence is relevant with respect to *Althen* prong one/*Loving* prong four. *See, e.g., D'Tiole v. Sec'y of Health & Hum. Servs.*, 2016 U.S. Claims LEXIS 2003 (Fed. Cl. Spec. Mstr. Nov. 28, 2016), *mot. for review den'd*, 132 Fed. Cl. 421 (2017), *aff'd*, 726 Fed.App'x 809 (Fed. Cir. 2018); *Blackburn v. Sec'y of Health & Hum. Servs.*, No. 10–410V, 2015 WL 425935, at *28–30 (Fed. Cl. Spec. Mstr. Jan. 9, 2015). However, this type of evidence is not required in order for a petitioner to establish that a vaccine can cause or significantly aggravate an injury.

In brief summary: Petitioner has presented evidence of the fertile field theory, although Fujinami did not discuss vaccines as a disease trigger. She has presented evidence from Frohman & Wingerchuk that immunization can trigger myelitis in the context of underlying disease; (although this one sentence has limitations, as discussed above). She has also presented a variety of case reports noting a temporal association between various vaccines and various CNS demyelinating diseases. In its totality this evidence is thin, especially when considered in the context of the literature presented by Respondent. In light of the above, I find that Petitioner has not provided a sound and reliable medical or scientific explanation for how the vaccines she

received could have significantly aggravated her MS. Accordingly, Petitioner has not met her burden under *Loving* prong four/*Althen* prong one.[14]

C. *Althen* Prong Three/*Loving* Prong Six

Due to the interplay between the fifth and sixth *Loving* prongs, I will address them out of order. *Loving* prong six requires Petitioner to establish a "proximate temporal relationship" between the significant aggravation of her condition and the vaccines she received. *Loving* at 144; *see also Althen*, 418 F.3d at 1281. Petitioner must offer "preponderant proof that the onset of symptoms occurred within a timeframe which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation." *de Bazan v. Sec'y of Health & Human Servs.*, 539 F.3d 1347, 1352 (Fed. Cir. 2008).

The timing prong contains two parts. First, Petitioner must establish the "timeframe for which it is medically acceptable to infer" significant aggravation and second, she must demonstrate that the onset of the significant aggravation occurred in this period. *Shapiro v. Sec'y of Health & Hum. Servs.*, 101 Fed. Cl. 532, 542-43 (2011), *recons. denied after remand on other grounds*, 105 Fed. Cl. 353 (2012), *aff'd without op.,* 503 F. App'x 952 (Fed. Cir. 2013). As it is uncontested, I will address the question of onset first.

Petitioner received the polio vaccine on April 4, 2016 and Tdap vaccine on April 22, 2016. She experienced onset of right-sided weakness on approximately June 3, 2016, two days prior to

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[14] As previously discussed, I have not considered the Langer-Gould study in my analysis of *Loving* prong four. In the event subsequent appeal renders this determination incorrect, I include my thoughts about the persuasive value of the article so as to prevent the need for an additional remand.

The Langer-Gould authors found a statistically significant increased risk of CNS acute demyelinating syndrome onset in patients under the age of 50 within 30 days of vaccination. Langer-Gould at 1509-10. These findings indicate that susceptible individuals can have a CNS autoimmune disorder triggered by vaccination. Even though Petitioner was older than 50, and developed CIS 42 days after vaccination, I would have found this study still provides support for her causation theory. I note that Petitioner's presentation was somewhat unusual in that she did not have her first clinical manifestation of MS until she was 67 years old. As the McDonald Criteria note, MS typically presents between the ages of 20 and 50. Between 0 and 5% have onset at age 60 or older. McDonald Criteria at 165. Accordingly, finding a study sufficiently powered to detect a statistically significant increase in MS onset in patients older than 60 would likely prove difficult. Indeed, Langer-Gould noted as a limitation that "the number of older individuals was relatively small." *Id.* at 1512. Petitioner's burden under *Loving* prong four/*Althen* prong one is to provide a sound and reliable medical or scientific explanation for how the vaccines at issue caused the significant aggravation of her injury. *Knudsen*, 35 F.3d at 548. The standard is not one of scientific certainty, "nor must the findings of the Court meet the standards of the laboratorian." *Bunting v. Sec'y of Health & Hum. Servs.*, 931 F.2d 867, 873 (Fed. Cir. 1991) (internal citation omitted). The study's broadly stated conclusion that "vaccines (like infections) may accelerate the transition from subclinical to overt autoimmunity in patients with existing disease" provides strong support for Petitioner's theory that the vaccines she received did just that. Langer-Gould at 1512. For those reasons, had I considered this study, I would have found that it, coupled with Fujinami, Frohman & Wingerchuk, and Petitioner's other evidence constitutes preponderant evidence in support of the fourth *Loving* prong.

her emergency room visit at Capital Health Regional Medical Center. Ex. 8 at 2. Onset of Petitioner's demyelinating disease therefore began 60 days after her polio vaccination and 42 days after her Tdap vaccination.

Special masters have determined that between 42 days and up to eight weeks is the outer limit of an appropriate temporal association between vaccination and the onset of a demyelinating disease of the central nervous system. *P.M. v. Sec'y of Health & Hum. Servs.*, No. 16-949V, 2019 WL 5608859, at *25 (Fed. Cl. Spec. Mstr. Oct. 31, 2019) (finding five days between vaccination and an MS relapse to be an appropriate temporal interval, and further citing the Rutschmann article, which found that five percent of 80 MS patients who experienced relapse did so within six weeks of receipt of flu vaccine); *Day v. Sec'y of Health & Hum. Servs.*, No. 12-630V, 2015 WL 8028393 (Fed. Cl. Spec. Mstr. Nov. 13, 2015) (finding persuasive a two to forty-two day risk interval established by the Risk Interval Working Group in a case of vaccine caused neuromyelitis optica); *Fisher v. Sec'y of Health & Hum. Servs.*, No. 99-432V, 2009 WL 2365459 (Fed. Cl. Spec. Mstr. July 13, 2009) (finding two months between hepatitis B vaccination and onset of optic neuritis eventually diagnosed as MS constituted an appropriate interval); *Pecorella v. Sec'y of Health & Hum. Servs.*, No. 04-1781V, 2008 WL 4447607 (Fed. Cl. Spec. Mstr. Sep. 17, 2008) (finding that two months between hepatitis B vaccination and onset of a TM is a medically appropriate interval to infer causation).

The Karussis & Petrou article supports the time frame of a CNS demyelinating process occurring within days of vaccination, but other clinical presentations can appear more than three weeks, and up to five months, post-vaccination. *See* Karussis & Petrou at 2. Karussis & Petrou identified 71 cases on PubMed involving a CNS demyelinating disease (to include MS) and vaccination. *Id.* In analyzing these 71 cases, researchers discovered that the mean time frame of onset was 14.2 days, however, a third of the 71 cases had onset after 3 weeks. *Id.* Among the MS results, some studies found a correlation between the Hepatitis B vaccine and a "significant risk for CIS or conversion to clinically definite MS." *Id.* at 3, 6. MS relapses are associated with some vaccines, including a ten-fold increase of relapse three months following yellow fever vaccination. *Id.* at 6.

Petitioner filed an article by Segal and Shoenfeld connecting CNS demyelinating processes to vaccines. Segal & Shoenfeld, *Vaccine-induced autoimmunity: the role of molecular mimicry and immune crossreaction*, 15 CELLULAR & MOLECULAR IMMUNOLOGY 586-94 (2018) (filed as Ex. 25) (hereinafter "Segal & Shoenfeld"). Of note, after the H1N1 vaccine was developed for the 2009 influenza pandemic, cases of narcolepsy and Guillain-Barré syndrome (GBS) rose, connecting vaccinations to neurological disorders. Segal & Shoenfeld at 588. The authors referenced a paper by Salmon et al., which "revealed a 2–3-fold increased risk of GBS in the 42 days following recipient of the 2009 influenza vaccines." *Id.* Although GBS is a demyelinating disease of the peripheral nervous system, the reference to Salmon's findings provides Petitioner with some support for her 42 day onset of CNS demyelinating symptoms post vaccination.

As additional support for the timing component of the case, Petitioner filed Agmon-Levin, which noted the connection between the Hepatitis B vaccine and TM as "within days to 3 months following inoculation." Agmon-Levin at 1200.

Given the wide spectrum of onset with CNS demyelinating diseases, I find that Petitioner has provided preponderant evidence that a CNS demyelinating process can occur within 60 days of vaccination and that Petitioner experienced symptoms consistent with a demyelinating process 42 days after receiving the Tdap vaccine and 60 days after receiving the polio vaccine. Petitioner has accordingly provided preponderant evidence in support of the sixth *Loving* prong.

D. *Althen* Prong Two/*Loving* Prong Five

Loving prong five/*Althen* prong two requires Petitioner to provide a logical sequence of cause and effect demonstrating that vaccination did cause a worsening of Petitioner's pre-existing condition. *Althen,* 418 F.3d at 1278; *Andreu,* 569 F.3d at 1375–77; *Grant,* 956 F.2d at 1148.

The evidence concerning whether Petitioner's Tdap and/or polio vaccines "did cause" a significant aggravation of her underlying condition presents a close issue. Often, the views of treating physicians provide persuasive evidence than can enable petitioners to meet this element of their case. The opinions of treating physicians are favored "as they are likely to be in the best position to determine whether a 'logical sequence of cause-and-effect show[s] that the vaccination was the reason for the injury." *Althen*, 418 F.3d at 1280. However, in this case, the opinions of Petitioner's treating physicians are of limited value. Each of the treating doctors who connected Petitioner's vaccination to her condition opined that the Tdap and/or polio vaccines caused her to develop ADEM, not MS. *See* Ex. 4 at 9 (Dr. Rao, noting Petitioner's diagnosis was "[l]ikely ADEM (Acute Disseminated Encephalomyelitis), probably related vaccination."); Ex. 50 at 4 (Dr. Bidwell, describing "[p]resumed ADEM following vaccination"); Ex. 51 at 58 (Dr. Baron, opining "[a]cute disseminated encephalomyelitis (primary encounter diagnosis) [i]n 2016, thought due to a vaccine."); Ex. 17 (Dr. Kam-Hansen, stating that "is highly likely that the two vaccinations she received in April of 2016 (polio and subsequently, the Tdap immunization she received on April 22, 2016) caused her to develop ADEM."). While Petitioner's showing constitutes some evidence in support of the "did cause" prong, this evidence carries limited weight.

In this case, the evidence of Petitioner's medical history is undisputed. Petitioner had clinically silent MS prior to vaccination. Forty-two days after receipt of the Tdap vaccine, she developed her first clinical episode of MS manifesting as a partial myelitis. Although the cause of MS is unknown, researchers believe that certain viruses are associated with the disease and often precede exacerbations. Fujinami at 84. Petitioner did not have any viral illnesses that would explain the clinical onset of her disease.

When a petitioner has established that vaccination can cause a given condition and has demonstrated that the timing prong has also been met, it allows the petitioner to establish that vaccination was a but-for cause of her condition. The Federal Circuit has provided guidance with respect to this issue. "Evidence demonstrating petitioner's injury occurred within a medically acceptable time frame bolsters a link between the injury alleged and the vaccination at issue under the "but-for" prong of the causation analysis." *See Capizzano,* 440 F.3d at 1326 (finding medical opinions that explain how a vaccine can cause the injury alleged coupled with evidence demonstrating a close temporal relationship "are quite probative" in proving actual causation). *Pafford,* 451 F.3d at 1358*; see also Contreras,* 107 Fed. Cl. at 295, (finding that there is a "logical overlap between the three *Althen* prongs, and that evidence that goes to one prong may also be probative for another prong").

Ultimately, however, my finding that Petitioner did not establish that the Tdap vaccine "can cause" a significant aggravation of MS, means that she cannot demonstrate that it did so in her specific case. *Harris v. Sec'y of Health & Hum. Servs.*, No. 10-322, 2014 WL 3159377 (Fed. Cl. Spec. Mstr. June 10, 2014), *mot. for rev. denied*, (Fed. Cir. 2014). Accordingly, Petitioner has not presented preponderant evidence in support of *Loving* prong five.

VII. CONCLUSION

Based on the evidence presented in this case, and for the reasons discussed in this decision, I conclude that Petitioner has not demonstrated that the Tdap and/or polio vaccines can cause a significant aggravation of MS. **Her petition is therefore DISMISSED. The clerk shall enter judgment accordingly.**[15] The Clerk's Office is instructed to provide this Decision to the assigned judge. *See* Vaccine Rule 28.1(a).

IT IS SO ORDERED.

s/ Katherine E. Oler
Katherine E. Oler
Special Master

[15] Pursuant to Vaccine Rule 11(a), the parties may expedite entry of judgment by each filing (either jointly or separately) a notice renouncing their right to seek review.